CLAIMS

What is claimed is:

1. A method of inhibiting cell proliferation in a tumor of a patient by orally administering a gastric retention solid dosage form or liquid composition containing irinotecan to the patient,

wherein the dosage form or liquid composition releases the irinotecan in the patient's stomach and at least a portion of the released irinotecan is converted into a metabolite before it is absorbed into the patient's bloodstream,

wherein the metabolite can exist in an active lactone form and an inactive hydroxy acid form,

wherein, the bioavailability of the lactone form of the metabolite is greater than the bioavailability of the lactone form of the metabolite when irinotecan is administered in a non-gastric retention solid dosage form or liquid composition, resulting in enhanced systemic delivery of the active form of the metabolite to the tumor.

2. The method of claim 1 wherein bioavailability is measured by the area under a curve of bloodstream concentration of the metabolite versus time.

3. The method of claim 2 wherein the relative bioavailability of the lactone form of the metabolite versus intravenous bioavailability, taken as the area under the bloodstream concentration curve for gastric retention administration divided by the area under the bloodstream concentration curve for intravenous administration, is about 0.5 or higher.

4. A method of inhibiting cell proliferation in a tumor of a patient by orally administering a gastric retention solid dosage form or liquid composition containing an antineoplastic agent that is susceptible to removal by the P-

glycoprotein efflux pump,

wherein the dosage form or liquid composition releases the antineoplastic agent in the patient's stomach,

wherein the biovailability of the antineoplastic agent is greater than the bioavailability when the antineoplastic agent is administered in a non-gastric retention solid dosage form or liquid composition, resulting in enhanced systemic delivery of the antineoplastic agent to the tumor.

5. The method of claim 4 wherein bioavailability is measured by the area under a curve of bloodstream concentration of the antineoplastic agent versus time.

6. The method of claim 4 wherein the antineoplastic agent is selected from the group consisting of etoposide, paclitaxel, doxorubicin and vincristine.

7. A solid pharmaceutical dosage form for enhanced systemic delivery of an antineoplastic agent comprising, as an active ingredient, an antineoplastic agent that is capable of absorption through the lining of the stomach, jejunum or duodenum of a patient and a gastric retention vehicle composition comprising a hydrogel, wherein the dosage form expands upon contact with gastric fluid and wherein after ingestion by a patient the gastric retention vehicle composition expands to retain the dosage form in the patient's stomach for a prolonged period of time.

8. The pharmaceutical dosage form of claim 7 wherein the antineoplastic agent is absorbable through the lining of the stomach and is susceptible to base induced deactivation.

9. The pharmaceutical dosage form of claim 8 wherein the antineoplastic agent is irinotecan.

10. A method of inhibiting cell proliferation in a tumor of a patient afflicted with metastatic carcinoma of the colon or rectum by orally administering a dosage form of claim 9 to the patient.

11. A method of inhibiting cell proliferation in a tumor of a patient afflicted with metastatic carcinoma of the colon or rectum by executing a therapeutic program of repeated oral administration of dosage forms of claim 9 to the patient.

12. The method of claim 11 wherein the dosage forms contain a unit dose of from about 20 to about 250 milligrams of irinotecan.

13. The pharmaceutical dosage form of claim 7 wherein the antineoplastic agent is susceptible to deactivation by the Pgp efflux pump of cells of the lining of the small intestine.

14. The pharmaceutical dosage form of claim 13 wherein the antineoplastic agent is selected from the group consisting of etoposide, paclitaxel, doxorubicin and vincristine.

15. The solid pharmaceutical dosage form of claim 14 wherein the antineoplastic agent is etoposide.

16. A method of inhibiting cell proliferation in a tumor of a patient afflicted with testicular tumors by orally administering a dosage form of claim 15 to the patient.

17. A method of inhibiting cell proliferation in a tumor of a patient afflicted with testicular tumors by executing a therapeutic program of repeated oral administration of dosage forms of claim 15 to the patient.

18. The method of claim 17 wherein the dosage forms contain a unit dose of from

about 25 to about 250 milligrams of etoposide.

19. A method of inhibiting cell proliferation in a tumor of a patient afflicted with small cell lung cancer by orally administering a dosage form of claim 15 to the patient.

20. A method of inhibiting cell proliferation in a tumor of a patient afflicted with small cell lung cancer by executing a therapeutic program of repeated oral administration of dosage forms of claim 15 to the patient.

21. The method of claim 20 wherein the dosage forms contain a unit dose of from about 25 to about 250 milligrams of etoposide.

22. The solid pharmaceutical dosage form of claim 14 wherein the antineoplastic agent is paclitaxel.

23. A method of inhibiting cell proliferation in a tumor of a patient afflicted with non-small cell lung cancer by orally administering a dosage form of claim 22 to the patient.

24. A method of inhibiting cell proliferation in a tumor of a patient afflicted with non-small cell lung cancer by executing a therapeutic program of repeated oral administration of dosage forms of claim 22 to the patient.

25. The method of claim 24 wherein the dosage forms contain a unit dose of from about 25 to about 250 milligrams of paclitaxel.

26. A method of inhibiting cell proliferation in a tumor of a patient afflicted with ovarian cancer by orally administering a dosage form of claim 22 to the patient.

27. A method of inhibiting cell proliferation in a tumor of a patient afflicted with

ovarian cancer by executing a therapeutic program of repeated oral administration of dosage forms of claim 22 to the patient.

28. The method of claim 27 wherein the dosage forms contain a unit dose of from about 25 to about 250 milligrams of paclitaxel.

29. A method of inhibiting cell proliferation in a tumor of a patient afflicted with breast cancer by orally administering a dosage form of claim 22 to the patient.

30. A method of inhibiting cell proliferation in a tumor of a patient afflicted with breast cancer by executing a therapeutic program of repeated oral administration of dosage forms of claim 22 to the patient.

31. The method of claim 30 wherein the dosage forms contain a unit dose of from about 25 to about 250 milligrams of paclitaxel.

32. The solid pharmaceutical dosage form of claim 7 wherein the gastric retention vehicle composition further comprises tannic acid.

33. The solid pharmaceutical dosage form of claim 7 wherein the gastric retention vehicle composition further comprises a superdisintegrant.

34. The solid pharmaceutical dosage form of claim 33 wherein the superdisintegrant is selected from the group consisting of crosspovidone, croscarmellose sodium, sodium starch glycolate and mixtures thereof.

35. The solid pharmaceutical dosage form of claim 33 wherein the hydrogel is selected from the group consisting of hydroxypropyl methylcellulose and mixtures of hydroxypropyl methylcellulose and hydroxypropylcellulose.

36. The solid pharmaceutical dosage form of claim 35 wherein the gastric retention vehicle composition comprises:

a) from about 20 to about 70 weight percent of the hydrogel, the hydrogel comprising hydroxypropyl methylcellulose and hydroxypropylcellulose in a weight ratio of from about 1:3 to about 5:3;

b) from about 25 to about 75 weight percent of the superdisintegrant; and

c) from about 2 to about 10 weight percent tannic acid.

37. The solid pharmaceutical dosage form of claim 36 wherein the gastric retention vehicle composition comprises:

a) from about 30 to about 55 weight percent superdisintegrant,

b) about 5±2 weight percent tannic acid, and

c) an amount of hydrogel sufficient to bring the total weight percent to 100.

38. The solid pharmaceutical dosage form of claim 36 wherein the gastric retention vehicle composition comprises:

a) from about 10 to about 20 weight percent hydroxypropyl methylcellulose,

b) from about 45 to about 50 weight percent hydroxypropyl cellulose,

c) from about 25 to about 35 weight percent sodium starch glycolate, and

d) from about 4 to about 10 weight percent tannic acid.

39. The solid pharmaceutical dosage form of claim 36 wherein the gastric retention vehicle composition comprises:

a) from about 10 to about 30 weight percent hydroxypropyl methylcellulose,

b) from about 40 to about 60 weight percent hydroxypropyl cellulose,

c) from about 7 to about 35 weight percent croscarmellose sodium, and

d) from about 4 to about 10 weight percent tannic acid.

40. The solid pharmaceutical dosage form of claim 7 wherein the prolonged period of time is about three hours or more.

41. The solid pharmaceutical dosage form of claim 40 wherein the prolonged period of time is about five hours or more.

42. The solid pharmaceutical dosage form of claim 7 wherein the gastric retention vehicle composition expands in volume at least about three fold.

43. The solid pharmaceutical dosage form of claim 42 wherein the gastric retention vehicle composition expands in volume at least about five fold.

44. The solid pharmaceutical dosage form of claim 43 wherein the gastric retention vehicle composition expands in volume at least eight about fold.

45. The solid pharmaceutical dosage form of claim 7 wherein the gastric retention vehicle composition expands to its fullest extent within about fifteen minutes.

46. The solid pharmaceutical dosage form of claim 45 wherein the gastric retention vehicle composition expands to its fullest extent within about five minutes.

47. The solid pharmaceutical dosage form of claim 7 in the form of a capsule comprising an acid degradable shell and the antineoplastic agent and gastric retention vehicle composition as filling.

48. The solid pharmaceutical dosage form of claim 7 wherein the dosage form is ovoid or elliptical in shape.

49. The solid pharmaceutical dosage form of claim 48 having dimensions of from about 4 mm to about 8 mm in two dimensions and from about 10 mm to about 20 mm in the third dimension.

50. The solid pharmaceutical dosage form of claim 49 having dimensions of about 6 mm by about 6 mm by about 16 mm.

51. A liquid pharmaceutical composition for enhanced systemic delivery of antineoplastic agents comprising, as an active ingredient, an antineoplastic agent that is capable of absorption through the lining of the stomach, jejunum or duodenum of a patient and a gastric retention vehicle composition comprising a gelling agent wherein after ingestion by the patient the gastric retention vehicle composition gels or precipitates to retain the dosage form in the patient's stomach for a period of three hours or more.

52. The liquid pharmaceutical composition of claim 51 wherein the gastric retention vehicle composition comprises a protein.

53. The liquid pharmaceutical composition of claim 52 wherein the protein is selected from the group consisting of serum albumin, oval albumin, casein and gelatin.

54. The liquid pharmaceutical composition of claim 51 wherein the gastric retention vehicle composition comprises a polysaccharide.

55. The liquid pharmaceutical composition of claim 54 wherein the gastric retention vehicle composition comprises a mixture of ethylhydroxyethylcellulose and a surfactant selected from the group consisting of cationic surfactants or anionic surfactants that are not extensively protonated in gastric fluid.

56. The liquid pharmaceutical composition of claim 55 wherein the surfactant is selected from the group consisting of hexadecyltrimethylammonium chloride, tetradecylbetainate chloride and hexadecylpyridinium chloride, sodium dodecyl sulfate, sodium dodecyl monoethyleneoxide sulfate, sodium dodecyl sulfonate, sodium dosdecyl phosphate, sodium dodecyl phosphonate and sodium *p*-

dodecylbenzene sulfonate.

57. The liquid pharmaceutical composition of claim 54 wherein the gastric retention vehicle composition comprises low methoxylated pectin and a divalent metal salt.

58. The liquid pharmaceutical composition of claim 57 wherein the low methoxylated pectin has a 20-50 percent degree of methoxylation and a 3-23% degree of amidation.

59. The liquid pharmaceutical composition of claim 57 wherein the divalent metal salt is calcium carbonate.

60. The liquid pharmaceutical composition of claim 54 wherein the gastric retention vehicle composition comprises methylcellulose.

61. The liquid pharmaceutical composition of claim 60 wherein the methylcellulose comprises 5% or more of the dosage form by weight.

62. The liquid pharmaceutical composition of claim 51 wherein the gastric retention vehicle composition comprises a mixture of from about 0.5 weight percent sodium alginate, from about 0.5 to about 3 weight percent of a natural polymer selected from the group consisting of xanthan gum, carrageenan and gelatin.

63. A method of inhibiting cell proliferation in a tumor of a patient afflicted with metastatic carcinoma of the colon or rectum by orally administering a liquid pharmaceutical composition of claim 51 wherein the antineoplastic agent is irinotecan.

64. A method of inhibiting cell proliferation in a tumor of a patient afflicted with metastatic carcinoma of the colon or rectum by executing a therapeutic program of

repeated oral administration of a liquid pharmaceutical composition of claim 51 wherein the antineoplastic agent is irinotecan.

65. The method of claim 64 wherein the liquid pharmaceutical composition is administered in a unit dose of from about 20 to about 250 milligrams of irinotecan.

66. A method of inhibiting cell proliferation in a tumor of a patient afflicted with testicular tumors by orally administering a liquid pharmaceutical composition of claim 51 wherein the antineoplastic agent is etoposide.

67. A method of inhibiting cell proliferation in a tumor of a patient afflicted with testicular tumors by executing a therapeutic program of repeated oral administration of a liquid pharmaceutical composition of claim 51 wherein the antineoplastic agent is etoposide.

68. The method of claim 67 wherein the liquid pharmaceutical composition is administered in a unit dose of from about 25 to about 250 milligrams of etoposide.

69. A method of inhibiting cell proliferation in a tumor of a patient afflicted with small cell lung cancer by orally administering a liquid pharmaceutical composition of claim 51 wherein the antineoplastic agent is etoposide.

70. A method of inhibiting cell proliferation in a tumor of a patient afflicted with small cell lung cancer by executing a therapeutic program of repeated oral administration of a liquid pharmaceutical composition of claim 51 wherein the antineoplastic agent is etoposide.

71. The method of claim 70 wherein the liquid pharmaceutical composition is administered in a unit dose of from about 25 to about 250 milligrams of etoposide.

72. A method of inhibiting cell proliferation in a tumor of a patient afflicted with ovarian cancer by orally administering a liquid pharmaceutical composition of claim 51 wherein the antineoplastic agent is paclitaxel.

73. A method of inhibiting cell proliferation in a tumor of a patient afflicted with ovarian cancer by executing a therapeutic program of repeated oral administration of a liquid pharmaceutical composition of claim 51 wherein the antineoplastic agent is paclitaxel.

74. The method of claim 73 wherein the liquid pharmaceutical composition is administered in a unit dose of from about 25 to about 250 milligrams of paclitaxel.

75. A method of inhibiting cell proliferation in a tumor of a patient afflicted with breast cancer by orally administering a liquid pharmaceutical composition of claim 51 wherein the antineoplastic agent is paclitaxel.

76. A method of inhibiting cell proliferation in a tumor of a patient afflicted with breast cancer by executing a therapeutic program of repeated oral administration of a liquid pharmaceutical composition of claim 51 wherein the antineoplastic agent is paclitaxel.

77. The method of claim 76 wherein the liquid pharmaceutical composition is administered in a unit dose of from about 25 to about 250 milligrams of paclitaxel.

78. A method of inhibiting cell proliferation in a tumor of a patient afflicted with non-small cell lung cancer by orally administering a liquid pharmaceutical composition of claim 51 wherein the antineoplastic agent is paclitaxel.

79. A method of inhibiting cell proliferation in a tumor of a patient afflicted with non-small cell lung cancer by executing a therapeutic program of repeated oral

administration of a liquid pharmaceutical composition of claim 51 wherein the antineoplastic agent is paclitaxel.